

II. **REMARKS**

The Office Action dated April 18, 2008, has been received and carefully noted. The amendments made herein and the following remarks are submitted as a full and complete response thereto.

Applicants thank the Examiner for reviewing the Information Disclosure Statement filed on September 20, 2004. However, Applicants note that the two non-patent references (Yuasa et al. "Application of Calcium Solid Preparation Adsorbing an Oily Medicine to Calcium Silicate," 1994, Vol. 42, No. 11, pp. 2327-2331; and Yuasa et al., "Studies on the Development of Intragastric Floating and Sustained Release Preparation," 1996, Vol. 44, No. 7, pp. 1361-1366) were not initialed by the Examiner. Applicants respectfully request that the Examiner review and initial the two references.

Claims 1-42 are pending. Claims 3, 10-18, and 21-42 have been withdrawn.

By this Amendment, claims 1, 5, and 6 are amended, and claim 4 has been canceled. Support for the amendment can be found in the specification and claims as originally filed. For example, claim 1 has been amended to incorporate the members of canceled claim 4. Further, claims 5 and 6 have been amended to correct typographical errors. Applicants submit that no new matter has been added and respectfully request reconsideration and withdrawal of the pending rejections.

Claims 1-9, 19 and 20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Tsuru et al. (EP 0 376 331) in view of Holmberg et al. (WO 01/66088). Applicants traverse the rejection.

Claim 1 of the presently claimed invention is directed to a "solid drug delivery composition comprising one or more NO-donating Non Steroidal Antiinflammatory

Compound(s) (NO-donating NSAID(s)) absorbed into porous particles, wherein the porous particles are selected from the group consisting of dibasic calcium phosphate, anhydrous, microcrystalline cellulose and pregelatinised starch or a mixture thereof" (emphasis added).

Applicants submit that Tsuru et al. discloses a "drug delivery granule capable of slowly releasing impregnated drug components" (page 2, lines 7-8). Applicants submit that although Tsuru et al. discloses that the granules can be "porous granules of a calcium phosphate compound having a Ca to P (Ca/P ratio) of 1.3 to 1.8..." (page 2, lines 48-50) (emphasis added), Tsuru et al. does not teach or suggest the presently claimed invention.

Applicants submit that dibasic calcium phosphate and dibasic calcium phosphate anhydrous have the general formula of $\text{CaHPO}_4 \cdot m\text{H}_2\text{O}$, wherein $0 \geq m \geq 0.5$. Therefore, the atomic ratio of Ca to P is 1, and when m is 0, the compound is Fujicalin® (dibasic calcium phosphate anhydrous). Applicants enclose information about Fujicalin®. Applicants note that dibasic calcium phosphate anhydrous was used in some of the Examples (see specification, page 23, line 23). Applicants submit that dibasic calcium phosphate and dibasic calcium phosphate anhydrous are different than the porous granules of Tsuru et al., which have an atomic ratio of Ca to P (Ca/P ratio) of 1.3 to 1.8.

Further, Applicants submit that Tsuru et al. also fails to teach or suggest the other porous particles of claim 1, in particular microcrystalline cellulose, pregelatinised starch, calcium silicate, and magnesium aluminometasilicate, or mixtures thereof. In addition, Applicants note that Tsuru et al. discloses "slow release drug delivery

granules," whereas some embodiments of the present invention provide a large percentage of drug released (see specification, pages 27-29).

Applicants submit that Holmberg et al. does not fulfill the deficiencies of Tsuru et al. For example, Applicants submit that Holmberg et al. discloses a pharmaceutical composition in the form of an emulsion pre-concentrate, comprising one or more NO-releasing NSAIDs, one or more surfactants, and optionally an oil or semi-solid fat (page 4, lines 6-12). Holmberg et al. discloses NO-releasing naproxen (formula (Ia), page 8). However, there is no *prima facie* case of obviousness with the combination of Holmberg et al. with Tsuru et al.

For at least the above reasons, Applicants submit that the presently claimed invention is patentable over Tsuru et al. and Holmberg et al. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-9, 19, and 20 under 35 U.S.C. § 103(a).

III. **CONCLUSION**

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event this response is not timely filed, the Applicants hereby petition for an appropriate extension of time. The fee for this extension, along with any other additional fees which may be required with respect to this response, may be charged to Deposit Account No. 01-2300, referencing Attorney Docket No. 026220-00054.

Respectfully submitted,



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Enclosure: Fujicalin® Information Sheet

FUJICALIN®

For Direct Compression

A Dramatic Advancement in Pharmaceutical Excipients

Innovation

Fuji Chemical introduces Fujicalin® - an innovative new Dibasic Calcium Phosphate Anhydrous (DCPA) for superior direct compression tabletting. Fujicalin provides significantly improved compressibility and flowability compared to conventional DCPA and Dibasic Calcium Phosphate Dihydrate (DCPD).

Fujicalin®'s superior characteristics are due in large part to its unique manufacturing process. Fuji has developed a method of producing Fujicalin® by first restricting the growth of the primary crystal during synthesis. This results in a submicron sized crystal. Whereas, the primary crystal size of conventional dibasic calcium phosphate is much coarser. This difference in crystal size is demonstrated in the two SEMs shown on this page. The process is completed with a spray drying step which results in the combining of these microcrystals into porous spheres with greatly reduced inter-particle friction. Consequently, Fujicalin® has demonstrated to have many superior and unique characteristics not normally found in conventional DCP excipient.

FEATURES THAT MAKE FUJICALIN® UNIQUE

1. Highly Compressible

Fujicalin® is harder than conventional excipients under direct compression pressure.

2. Easy Blending and High Flowability

Fujicalin®'s spherical shape creates less friction so there is superior flowability.

3. Excellent Tablet Disintegration

Fujicalin® works with other disintegrants to promote rapid disintegration regardless of tablet hardness.

4. Non-Abrasiveness

Unlike the hard and rough granules of dicalcium phosphate dehydrate, Fujicalin® granules have a smooth surface and are not abrasive.

5. Oil Adsorption Capability

Fujicalin®'s high degree of porosity is retained even under high pressure, resulting in excellent oil adsorbing capability.

6. Flexibility

Fujicalin® is approved for pharmaceutical and food excipient use.

PROVEN SUPERIORITY IN:

Compressibility

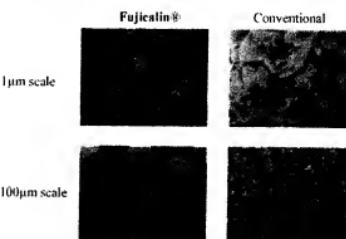
Fujicalin® consistently shows comparable hardness under any compression pressure as shown in Figure 1. Unlike the hard, non-

Micrometric properties of Fujicalin®, conventional DCPA and DCPD

Property	Fujicalin®	DCPA	DCPD
Mean particle size (μm)	0.15	45	127
SGT density (mg/ml)	0.43	0.76	0.83
SGT density required (g/ml)	0.05	0.78	0.91
Angle of repose ($^\circ$)	30	42	36
MT specific surface area (m^2/g)	40	1.65	0.87
Oil adsorption capacity (mg/g)	1.1	0.4	0.2
Water adsorption capacity (ml/g)	1.2	0.6	0.2
Loss on drying (%)	0.5	—	0.8

*One method DCPA=dibasic calcium phosphate anhydrous, DCP=dibasic calcium phosphate dihydrate

Scanning Electron Microphotographs of Fujicalin® and Conventional Dibasic Calcium Phosphates



Chemical Formula

CaHPO_4 - Dibasic Calcium Phosphate;
Calcium Hydrogen Phosphate

Pharmacopoeia & Regulatory Issue

Fujicalin® conforms to USP/NF, EP, and JP. Dibasic calcium phosphate anhydrous or calcium hydrogen phosphate is also applicable for food use. US DMF Type IV filed in 1998.

Listed as GRAS (Generally Recognized As Safe)